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(57) Abstract

A pharmaceutical composition including an active anticonvulsant drug and an effective amount of at least one metabolite of dextromethorphan sufficient to potentiate the anticonvulsant activity of the anticonvulsant drug. The metabolites and in particular dextrorphan are effective in potentiating the activity of anticonvulsants including phenytoin and carbamazepine. A method of treating epilepsy and other forms of convulsions comprising administration either simultaneously or sequentially and of an effective amount of an anticonvulsant drug and at least one of the dextromethorphan metabolites in an amount sufficient to potentiate the action of the anticonvulsant drug.

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DEXTRORPHAN POTENTIATOR FOR ANTICONVULSANT COMPOSITION AND METHOD

Cross-Reference to Related Application

The present application is related to co-pending application entitled DEXTROMETHORPHAN POTENTIATOR FOR ANTICONVULSANT COMPOSITIONS AND METHOD, S.N. _____ filed concurrently herewith.

BACKGROUND OF THE INVENTION

Field Of The Invention

The present invention relates to a novel composition and a method for the treatment of epilepsy and other forms of convulsions. More specifically, the invention is directed to a pharmaceutical composition comprising the metabolites of dextromethorphan as a potentiating agent for an anticonvulsant drug.

Description Of The Prior Art

Efforts have been made in the field of medicine with varying success in treating epileptic seizures and other convulsions. Most types of seizures, including generalized or focal seizures, can be treated with one of several anti-epileptic drugs. One of the more commonly used anti-epileptic drugs is diphenylhydantoin (DPH), often referred to as phenytoin.

The popularity in using phenytoin stems from its ability to inhibit epileptic activity without causing a general depression of the central

nervous system. Phenytoin also has the advantage in that it can limit the development of maximal seizure activity and reduce the spread f the seizure process from an active focus.

The use of many anticonvulsants, including phenytoin is limited, however, since the most effective anticonvulsants are toxic at some concentrations. Although the effectiveness of phenytoin in treating seizures increases with dosage, the adverse toxic effects also increase to an unacceptable and often times dangerous level. Many of these adverse toxic effects further increase with the length of exposure and vary with the mode of administration thereby further limiting the use of the anticonvulsant and necessitating the careful monitoring of the patient and medication procedures.

The dose-dependent toxic effects associated with the continued use of phenytoin as well as other anticonvulsant hydantoins, include cerebellar vestibular effects (nystagmus, ataxia and diplopia vertigo) and central nervous system disturbances such as blurred vision, mydriasis and hyperactive tendon reflexes. Behavioral changes that have been associated with the use of phenytoin include hyperactivity, confusion, dullness, drowsiness and hallucination. Further adverse toxic effects include increased frequency of seizures, peripheral neuropathy, gastrointestinal distress, gingival hyperplasia, osteomalacia, megaloblastic anemia, hirsutism, endocrine effects and lymphadenopathy. At very high doses, especially when administered intravenously, phenytoin can cause cardiovascular collapse and depression of the central nervous system.

In view of the adverse side effects, efforts have been made to develop an anti-epileptic drug or anticonvulsant agent having as few side effects as possible while maintaining efficacy. One such effort has been reported by T rtella in Brain Res., 383:314-318, 1986.

Tortella, aided by earlier work, discovered that dextrometh rphan could s rve as an effective anticonvulsant, possessing an activity similar to that f phenyt in. Dextromethorphan is a known p tent antitussive agent which has been used for many years in the medical field with few side effects. Most often, dextromethorphan is one of the active ingredients in over-the-counter cough and cold medication. Dextromethorphan is the non-narcotic d-stereo-isomer (enantiomer) of the opioid L-3-methoxy-17-methylmorphinan.

Tortella showed that 30 mg/kg dextromethorphan administered s.c. to rats could provide complete protection against transauricular maximal electroshock seizures. In addition, it was demonstrated that the anticonvulsant potency of phenytoin was potentiated by co-administration of dextromethorphan and that this potentiating effect was present even at sub-threshold levels of dextromethorphan (e.g., 15 mg/kg s.c.). Compounds which are related to dextromethorphan, or which inhibited the specific binding of [^{3}H]dextro-methorphan to this central nervous system site with nanomolar potencies (IC_{50} < 75 nM), were also found to be effective potentiating agents for phenytoin. As a result, the minimum effective dosage of phenytoin could be reduced which would reduce the dose-dependent side effects associated with phenytoin administration.

The discovery by Tortella was based, in part, on earlier findings reported by Craviso and Musacchio in Mol. Pharmacol., 23:619-628 and 23:629-640 (1983). This study was conducted in part to determine whether dextro-methorphan binds at a subset of opiate receptors. Craviso and Musacchio demonstrated high affinity binding of [^{3}H]dextromethorphan to homogenates of guinea pig, mouse and rat lower brainstem (K_d less than 20 nM). Of significant importance is that piate antag nists and agonists, and the dextromethorphan metab lite, dextrorphan, did not compete effectively

(K_i > 100 nM) at the dextromethorphan site. However, as noted above, it was shown that some antitussants including carbetapentane, caramiphen and dimethoxanate inhibited binding with IC_{50}'s in the 1 - 75 nM range. The report further revealed that the binding of [^{3}H]dextromethorphan was effectively inhibited <u>in vitro</u> by certain phenothiazines, neuroleptics, dextromethorphan analogs, antidepressants, antihistamines, muscarinic agents and calcium channel blockers. However, the primary importance of their work was in the discovery that the <u>in vitro</u> binding of [^{3}H]dextromethorphan to the central nervous system site was markedly increased in the presence of certain compounds including the antitussant noscopine and the anticonvulsant phenytoin. It was noted, however, that the anticonvulsants carbamazepine, diazepam, phenobarbital and ketamine did not enhance [^{3}H]dextromethorphan binding. The research also fell short in that it was unable to predict which of these compounds were capable of enhancing [^{3}H]dextromethorphan binding and which were not able to enhance binding.

Thus, the discovery of Tortella and Musacchio (U.S. Patent No. 4,694,010) of the potentiating characteristics of dextromethorphan as an anticonvulsant was based on the binding site of [^{3}H]dextromethorphan, and on the compounds, like dextromethorphan, which inhibited binding at the same site at concentrations considered reasonable to those skilled in the art (IC_{50} < 500 nM). The discovery of Tortella and Musacchio was, however, rather narrow since [^{3}H]dextromethorphan and the related non-opiate compounds were believed to be able to potentiate only the anti-epileptic hydantoin anticonvulsants which enhanced binding to the dextromethorphan site in the central nervous system. Of particular importance, of the excluded anticonvulsant compounds are anticonvulsants such as carbamazepine, phenobarbital, diazepam and ketamine which were specifically shown not to inhibit or enhance [^{3}H]dextromethorphan

binding. Still more important in the context f the present discovery, the number of suitable potentiating compounds was also limited by the requirements that the potentiators are non-opi id comp unds that act at the same binding site as dextromethorphan. Thus, related compounds that do not inhibit or enhance [^{3}H]dextromethorphan binding were excluded.

It has been known that dextromethorphan is rapidly metabolized in vivo via oxidative O-demethylation to yield dextrorphan (DEX) and two lesser metabolites. The minor N- and N,O-demethylation metabolite products are (+) D-(3) methoxymorphinan and (+) D-hydroxymorphinan respectively. In rats, dogs and humans the ratio of dextrorphan to dextromethorphan in plasma and urine typically exceeds 100 to 1. The absolute plasma levels of dextromethorphan following administration of 20 to 60 mg p.o. in humans rarely exceeds five nanograms per milliliter whereas the dextrorphan levels are 380 nanograms per milliliter. In man, dextrorphan represents the major metabolite since, in eight hours, the other demethylation products in urine account for less than 15% of the dose of dextromethorphan administered. More importantly, the major metabolite, dextrorphan, has a relatively low affinity (> 2000 nM) for the [^{3}H]dextromethorphan receptor but a relatively high affinity for the [^{3}H]TCP-labeled-NMDA-linked receptor (< 10 nM).

Since dextromethorphan is rapidly converted to dextrorphan in vivo these data raise the possibility that dextromethorphan's anticonvulsant effects may not be directly related to the [^{3}H]dextromethorphan binding site as suggested by Tortella and Musacchio, but may result from the action of metabolites at other (e.g., PCP/NMDA) receptors.

The present invention is directed primarily to the discovery that the metabolites of dextromethorphan which do not bind with reasonable affinity at the dextromethorphan r ceptor site (IC_{50} > 100 nM) can act as an effective

potentiator for anticonvulsants, including both those like phenytoin, that enhance [^{3}H]dextromethorphan binding and those that do not inhibit or enhance [^{3}H]dextromethorphan binding (e.g., carbamazepin , phenobarbital, diazepam, ketamine). In addition, the present invention relates to a composition of matter and a method of treating epilepsy using the metabolite of dextromethorphan as a potentiating agent for anticonvulsants.

SUMMARY OF THE INVENTION

The disadvantages and limitations of the prior art compositions and methods of treatment of epilepsy and other convulsions are obviated while reducing the adverse side effects of the prior art anticonvulsants and providing effective anticonvulsant treatment.

The present invention is directed primarily to a composition of matter including at least one metabolite of dextromethorphan as a potentiator for an anticonvulsant agent. More particularly the invention relates to a pharmaceutical composition which utilizes the metabolites of dextromethorphan as the potentiating agent for any anticonvulsant. The invention further relates to a method of treating epilepsy using the composition including an effective amount of potentiating agent of one of the metabolites of dextromethorphan and an anticonvulsant agent.

DESCRIPTION OF THE PREFERRED EMBODIMENT

The present invention is directed to the discovery that the metabolites f dextr methorphan and in particular the major metabolite, dextrorphan, are useful as anticonvulsants in the treatment of epilepsy. Moreover, the

present invention relates t the discovery that the metabolites of dextromethorphan are effective potentiating agents for ther anticonvulsant compounds. Specifically the metab lites of dextrom th rphan hav been shown to potentiate and increase the effectiveness of anticonvulsants and also to interact with PCP-linked-NMDA receptors.

In the preferred embodiment the dextromethorphan metabolite is intermixed in a potentiating amount, or administered separately as an adjunct, with a suitable anticonvulsant. The compounds are introduced to the patient in an amount necessary to treat epilepsy and prevent or control convulsions.

Dextromethorphan, [(+) 3-methoxy-17-methylmorphinan] is a widely used non-opiate antitussant which has recently been shown to possess anticonvulsant activity against electrical seizure in laboratory animals. Dextromethorphan is known to have has a high affinity for the [^{3}H]dextromethorphan labeled receptor but a relatively low affinity for the PCP receptor sites.

Dextromethorphan when introduced to the human body rapidly metabolizes into three metabolites. The major O-demethylated metabolite is dextrorphan (DEX), D(+)-17-methylmorphinan-3-ol. The minor metabolites by the N, and N,O-demethylation process are (+)D-3 methoxymorphinan, and (+)D-hydroxymorphinan.

Dextrorphan demonstrates a low affinity for the [^{3}H]dextromethorphan receptor (IC_{50} = 140 - 5000 nM) but a very high affinity for the PCP-labeled NMDA-linked receptor (IC_{50} < 10 nM). Since dextrorphan functions by a different mechanism, and binds at different sites than dextromethorphan, dextrorphan provides an additional approach to control and prevent convulsions in patients affected with seizure disorders. Additionally, we have discovered that dextrorphan can be used in a manner by which the anticonvulsant properties of other anticonvulsants can be improved or

p tentiated at lower d sages thereby providing a lowering of the chronic toxicity f the drugs.

Examples of the more commonly employed anticonvulsants include phenytoin, amobarbital sodium (sodium 5-ethyl-5-isopentylbarbiturate), methsuximide (N,2-Dimethyl-2-phenylsuccinimide), clonazepam (5-(2 chlorophenyl)-1, 3-dihydro-7-nitro 2H-1,4, benzodiazepine-2-one), valproic acid, metharbital (5,5 diethyl-1-methylbarbituric acid), mephobarbital (5-ethyl-1-methyl-5-phenylbarbituric acid, mephenytoin (3-methyl 5,5-phenyl-ethyl-hydantoin), primidone, paramethadione (5-ethyl-3,5-demethyl-2,4-oxazolidinedione, phenacemide (N-aminocarbonyl)-benzeneacetamide, trimethadione (3,5,5-trimethyloxozolidine-2,4-dione), diazepam (7-chloro-1,3-dihydro-1-methly-5-phenyl-2H-1,4 benzodiazepine-2-one) and ethosuximide (alpha-ethyl-alpha-methly succinimide) and carbamazepine.

The preferred anticonvulsants according to the invention are phenytoin or carbamazepine. It has been discovered that by simultaneously administering these different types of anticonvulsants with the metabolites of dextro-methorphan the effects of the anticonvulsants can be potentiated to reduce the required amount for effective treatment.

EXAMPLE I

Dextrorphan Protection Against MES Seizures

In order to determine the anticonvulsant activity of dextrorphan a series of experiments were carried out using standard laboratory techniques. Male CF-1 mice (27-34 g) were randomly assigned to a control group or drug treatment group. All the animals tested were naive to drug and seizure exposure and each animal was used only once. Each test group was comprised of a minimum of 8 test animals.

The first study was conducted using a standard maximal electr shock (MES) procedure for mice. A transauricular square wave shock of 50 mA, 0.6 msec/pulse, 100 pulses per second was applied for 0.2 seconds. Pilot studies indicated that these parameters produce reliable tonic-clonic seizures in 100 percent of the mice treated with an appropriate vehicle. Ethosuximide was determined to be ineffective in protecting against these seizures since only one in five mice was protected at one half hour and none was protected one hour after i.p. injections of 500 mg/kg. At this dose all mice injected showed signs of sedation, ataxia and gross toxicity.

The first study compared the effects of dextrorphan, dextromethorphan and phenytoin. Dextrorphan and dextromethorphan were dissolved in saline. Phenytoin was dissolved in 30% propylene glycol in distilled water. Dextrorphan and dextromethorphan were administered 30 min and phenytoin 1 hr prior to the MES test. All injections were i.p. in a volume of 0.01 ml/g.

Dextrorphan, like phenytoin and dextromethorphan, is shown in Table 1 to be a potent and efficacious anticonvulsant against MES seizures. The anticonvulsant effects of the dextrorphan were dose-related having an ED_{50} of 12.7 mg/kg. At higher doses, dextrorphan decreased the incidence of tonic hindlimb extension to 0%. When compared on the basis of molecular weight, dextrorphan was 2.2 times more potent than dextromethorphan as an anticonvulsant against MES seizures.

Table 1

DETERMINATION OF THE ANTICONVULSANT EFFECTS OF DEXTROMETHORPHAN, DEXTRORPHAN AND PHENYTOIN FOLLOWING I.P. ADMINISTRATION TO MICE

	Dextrorphan	Dextromethorphan	Phenytoin
ED_{16}	6.9	20.8	2.1
ED_{50}	12.7 (10.5-15.5)	29.2 (24.1-35.4)	5.5 (3.2-9.3)
ED_{84}	23.5	41.1	14.3

Based on at least 8 doses for each drug, covering the entire range from 0 to 100% protection, $n \geq 8$ mice per dose. Values in parenthesis are 95% confidence limits calculated according to the method of Litchfield and Wilcoxon (1949, J. Pharmacol. Exp. Therap., 49:99). All values are reported as mg/kg.

EXAMPLE II

Dextrorphan vs Dextromethorphan Reversal of N-methyl-D-aspartate Seizures

In order to determine if the anticonvulsant activity of dextrorphan extended to seizure models other than that induced by maximal electroshock, the potency of dextrorphan to antagonize N-methyl-D-aspartate (NMDA)-induced convulsions was examined. NMDA is a potent excitatory amino acid analog which when administered to animals elicits a characteristic seizure response. The experiments were warranted based on prior observations that dextrorphan has a high affinity for phencyclidine (PCP) receptors in vitro and that PCP and related compounds are potent antagonists of NMDA-induced neuroexcitation. Note that compounds that do not interact with PCP or NMDA receptors do not block NMDA-induced seizures. Thus, dextrorphan and dextromethorphan would not be predicted to be effective anticonvulsants in this model based on the prior discovery of Musacchio and Tortella.

Male CF-1 mice weighing 25 - 30 grams were used for all studies. All of the test animals were naive to drug and seizure exposure and were used only once. Compounds of interest were dissolved in saline (0.9%; w/v) and administered i.p. in a final volume of 1 percent of body weight. Test compounds (anticonvulsants) were administered 30 minutes prior to the induction of seizures. Seizures were induced by the administration of NMDA (250 mg/kg) and animals were observed for a period of thirty minutes. Typically, control animals responded with seizure activity consisting of initial staring followed in rapid order by hindlimb scratching, increased locomotor activity, rearing behavior, clonic seizures, tonic extension and death. In animals developing seizures, the entire episode evolved in 7 - 11 minutes. Compounds that prevented the t nic-clonic seizure activity were judged to have enticonvulsant effects.

Referring t Table 2, MK801 was the m st effective compound evaluated to antag nize NMDA-induced seizures and, on a mole basis was 7-fold m re potent than PCP. The order of potency of the remaining compounds was PCP > 3-(2-carboxypiperazin-4-yl)propyl-1-phosphonic acid (CPP) > ketamine = dextrorphan = dextromethorphan > DL(±)2-amino-7-phosphonoheptanoic acid (AP7). Of importance, dextrorphan was equipotent to the clinically useful dissociative anesthetic, ketamine, 11-fold less potent than the direct acting NMDA receptor antagonist, CPP, and 4 to 5-fold more potent than the prototypical NMDA receptor antagonist, AP7.

Table 2

POTENCY OF VARIOUS COMPOUNDS TO INHIBIT NMDA-INDUCED SEIZURES

Measure	MK801	PCP	CPP	KET	DEX	AP7
			(mg/kg; free drug)			
ED_{16}	0.024	0.04	1.1	4.8	12.4	50
ED_{50}	0.085 (0.067-0.137)	0.64 (0.32-1.38)	2.2 (1.5-3.1)	17 (8-35)	26 (17-40)	107 (70-165)
ED_{84}	0.38	9.9	4.2	61	56	229

Methods have been described in the text. Values shown in parentheses are the ninety-five percent confidence intervals calculated according to the method of Litchfield and Wilcoxon (1949, J. Pharmacol. Exp. Therap., 49:99). The corresponding ED_{50}'s for the various drug calculated as the mole amount of the free compound and expressed as umoles were as follows: 0.38, MK801; 2.7, PCP; 9.7, CPP, 72, KET; 102, DEX; 103, DM, 475, AP7.

Abbreviations: PCP, phencyclidine; CPP, 3-(2 carboxy-piperazin-4-yl)propyl-1-phosphono acid; KET, ketamine; DEX, dextrorphan; DM, dextromethorphan.

To demonstrate that this action of dextrorphan and dextromethorphan and other PCP-like compounds was not a nonspecific effect related to anticonvulsants in general, a number of reference compounds that block convulsions in other animal models were tested for potency to antagonize NMDA-induced convulsions. All compounds were tested at doses previously shown by others to antagonize convulsions and were found to be devoid of activity. These included the clinically useful anticonvulsants phenytoin (60 mg/kg), phenobarbital (30 mg/kg), valproic acid (300 mg/kg) and diazepam (10 mg/kg). Also found to be ineffective were the $GABA_A$ receptor agonists muscimol (5 mg/kg) and THIP (15 mg/kg), the $GABA_B$ receptor agonist, baclofen (20 mg/kg), as well as the anticholinergic, atropine sulfate (10 mg/kg). Other compounds which inhibit seizures but were not able to inhibit NMDA-induced convulsions were two antitussives agents including the dextromethorphan receptor active agents, caramiphen (100 - 500 mg/kg) and noscapine (100 - 400 mg/kg).

Notwithstanding the observation that dextromethorphan and dextrorphan were moderately potent anticonvulsants when tested in the NMDA-seizure model, both agents demonstrated effectiveness to block the chemically-induced convulsions and death in test animals. Furthermore, the potency of the compounds to antagonize convulsions involving activation of receptors for excitatory amino acids was similar to the potency to attenuate MES-induced seizures. Thus, these data reveal that dextromethorphan and dextrorphan possess a broad spectrum of anticonvulsant activity that is dissimilar to standard reference agents.

EXAMPLE III

Dextrorphan Potentiator

The ability of dextrorphan to enhance and potentiate the effects of anticonvulsants was examined using the MES seizure model described in Example I, above. Male CF-1 mice weighing approximately 27-34 grams were randomly assigned to control or drug treatment groups. All of the test animals were naive to drug and seizure exposure and used only once. Dextrorphan was dissolved in saline and phenytoin in 30% propylene glycol in distilled water as described above. For combination studies phenytoin was administered 1 hr and dextrorphan 30 min prior to the test.

Table 3 shows that dextrorphan potentiated the anticonvulsant effects of phenytoin. Thus, the amount of protection (% animals without seizures) at any given dose of phenytoin was increased by co-administration of dextrorphan. For example, 9 mg/kg dextrorphan (a dose marginally effective when administered alone) increased the % protection from 0 to 37.5 at 0.25 mg/kg phenytoin, from 4.2 to 50 at 1 mg/kg phenytoin, and from 8.3 to 100 at 3.5 mg/kg phenytoin. Overall, the median effective dose (ED_{50}) of phenytoin was decreased almost 7-fold from 5.5 to 0.81 mg/kg.

Table 3

DEXTRORPHAN POTENTIATION OF THE ANTICONVULSANT EFFECTS OF PHENYTOIN

Dose Phenytoin (mg/kg)	% Protected		
	Phenytoin	Phenytoin + 6 mg/kg Dextrorphan	Phenytoin + 9 mg/kg Dextrorphan
0.25	0.0	25.0	37.5
1.0	4.2	37.5	50.0
2.0	6.25	25.0	37.5
3.5	8.3	37.5	100.0
4.0	33.0	50.0	
5.0	37.5	87.5	
6.0	62.5		
7.5	100.0		
ED_{50}	5.5 (3.2-9.3)	2.6* (0.91-7.5)	0.81* (0.27-2.5)

*Significantly different from phenytoin, $p < 0.5$.

In summary, the foreg ing examples demonstrate that the dextromethorphan metabolite dextrorphan is a p tent anticonvulsant when administered alone in both the MES and N-methyl-D-aspartate models, and effectively potentiates the anticonvulsant effects of phenytoin in the MES model. These findings are contrary to the original discovery of Musacchio and Tortella in that (1) the present data demonstrates a potentiating action by a dextromethorphan metabolite that does not effectively inhibit [^{3}H]dextromethorphan binding, and (2) the anticonvulsant effect in the N-methyl-D-aspartate model indicates an action related to phencyclidine-labeled/N-methly-D-aspartate-linked receptors, rather than [^{3}H]dextromethorphan labeled receptors. This latter finding suggests that other dextromethorphan metabolites may also be effective anticonvulsants, regardless of whether they compete at dextromethorphan receptors, and also suggests that the range of anticonvulsants that can be potentiated by dextromethorphan or its metabolites may include compounds like carbamazepine that do not interact with dextromethorphan receptors.

Thus, in the preferred form of the invention a metabolite of dextro-methorphan is administered as the potentiating agent with an anticonvulsant drug. Any anticonvulsant may be used but phenytoin or carbamazepine are preferred. Although simultaneous administration in one dosage form is preferred, the compounds may be introduced sequentially or in any order necessary to achieve the optimal control of seizures. The preferred form of administration is oral but any medically accepted route of administration may be employed.

The novel composition according to the present invention is used primarily f r treatment f convulsions and in particular epilepsy. In the preferred f rm of the invention at least one of the metabolites of dextromethorphan is

combined with an anticonvulsant in a proportion whereby the effectiveness f the antic nvulsant is p tentiated. By potentiating the anticonvulsant effects the amount of the anticonvulsant can be reduced which reduces the dose-related side effects associated with continued use of standard anti-convulsants without sacrificing the efficacy.

The type and severity of the convulsions experienced by the patient will determine the amount of the combination administered. The ratio of the potentiating agent to the anticonvulsant and the effectiveness of the anticonvulsant will determine the amount and form of the composition to be administered to the patient.

The form of the anticonvulsants according to the present invention can be a liquid oral dose in the form of solutions and suspensions. In making solutions and suspensions the active ingredients are generally dissolved or suspended in distilled water containing a small amount of alcohol to facilitate suspension. Additionally, conventional syrup formulations or any other pharmaceutically acceptable liquid carrier may be employed.

When parenteral administration is the preferred method of introducing the anticonvulsants to the patient the compounds are dissolved in a suitable liquid carrier. The preferred carrier liquid is polyethylene glycol and alcohol although others may be used which are known by those skilled in the art.

Alternatively the anticonvulsants may be introduced as an oral dose in a solid form such as a tablet, pill or capsule. The tablets or capsules may be coated as desired to allow the tablets to be easily swallowed and to provide flavoring. Coatings commonly employed in the pharmaceutical industry may be applied from aqueous suspensions of sugar and insoluble powders such as starch, calcium carbonate, talc and titanium dioxide suspended with a

suitable mixing agent such as gelatin. Additional coatings may be applied as desired including water s luble dispersible material such as hydroxy-methylcellulose, cellulose, methylcellulose, carboxymethyl cellulose and mixtures of cellulose acetate and polyethylene glycol. In addition, the suitable dosage form may be a capsule formed from commonly employed materials.

In oral dosage form, the components are generally compounded with inert fillers such as talc, lactose, starch, bentonite, diatomaceous earth, lubricants and food flavorings. The tablets are generally formed by conventional procedures including compression molding.

The detailed description of the invention is provided primarily for the purpose of illustrating the preferred embodiment of the invention. It will be recognized by those skilled in the art that the preferred embodiment is not intended to limit the present invention to the particular compositions and methods as they may be readily modified by those skilled in the art. It will be further apparent that numerous other modifications not mentioned herein can still be made without departing from the spirit and scope of the invention as described in the following claims.

Claims:

1. An anticonvulsant pharmaceutical composition comprising;

(a) an effective amount of at least one metabolite of dextromethorphan; and

(b) an effective amount of an anticonvulsant compound.

2. The anticonvulsant pharmaceutical composition of claim 1 wherein said metabolite is from the demethylation of dextromethorphan.

3. The anticonvulsant pharmaceutical composition of claim 2 wherein the metabolite is dextrorphan.

4. The anticonvulsant pharmaceutical composition of claim 2 wherein said metabolite is (+)-D-3-methoxymorphinan.

5. The anticonvulsant pharmaceutical composition of claim 2 wherein said metabolite is (+)-D-hydroxymorphinan.

6. The anticonvulsant pharmaceutical composition of claim 1 wherein said anticonvulsant compound is a hydantoin anticonvulsant.

7. The anticonvulsant pharmaceutical composition of claim 6 wherein the anticonvulsant compound is phenytoin.

8. The anticonvulsant pharmaceutical composition of claim 1 wherein said anticonvulsant compound is an excitatory amino acid antagonist.

9. The anticonvulsant pharmaceutical composition of claim 1 wherein said anticonvulsant is (+)-5-Methyl-10,11-dihydro-5H-dibenzo[a,d] cyclohepten-5,10-imine.

10. The anticonvulsant pharmaceutical composition of claim 1 wherein said anticonvulsant compound is carbamazepine.

11. The anticonvulsant pharmaceutical composition of claim 1 wherein said anticonvulsant is selected from the group consisting of phencyclidine, 3-(2 carboxypiperazin 4-yl) propyl-1-phosphonic acid and ketamine.

12. A method of treating epilepsy and other convulsions including the step of administering to a patient an effective amount of a pharmaceutical composition comprising:

(a) an effective amount of at least one anticonvulsant compound; and

(b) at least one metabolite of dextromethorphan in an amount sufficient to potentiate the anticonvulsant effects of said anticonvulsant compound.

13. The method according to claim 10 wherein said anticonvulsant compound is a hydantoin.

14. The method according to claim 13 wherein said hydantoin is phenytoin.

15. The method according to claim 10 wherein said anticonvulsant compound is carbamazepine.

16. The method of claim 10 wherein said anticonvulsant compound is an excitatory amino acid antagonist.

17. The method of claim 16 wherein said excitatory amino acid antagonist is (+)-5-Methyl-10, 11-dihydro-5H-dibenzo [a,d] cyclohepten-5, 10-imine.

18. The method of claim 10 wherein said metabolite is dextrorphan.

19. The method of claim 12 wherein said metabolite is selected from the group comprising (+)-D-3-methoxymorphinan and (+)-D-hydroxymorphinan.

20. A method of treating and controlling seizures in an animal in need f treatment comprising:

(a) administering to said animal an effective amount of an anticonvulsant; and

(b) administering to said animal a potentiating amount of at least one metabolite of dextromethorphan selected from the group comprising dextrorphan, D-3 methoxymorphinan and D-hydroxymorphinan.

21. The method of claim 20 wherein said anticonvulsant composition is carbamazepine.

22. The method of claim 20 wherein said anticonvulsant composition is phenytoin.

23. The method of claim 20 wherein said anticonvulsant does not have a high affinity (i.e., K_i > 100 nM) for the dextromethorphan receptor binding site.

24. The method of claim 20 wherein said anticonvulsant has a high affinity (K_i < 100 nM) for the dextromethorphan receptor binding site.

25. An anticonvulsant composition comprising:

(a) at least one anticonvulsant compound selected from the group consisting of carbamazepine, hydantoins and excitatory amino acid antagonists; and

(b) at least one metabolite from the demethylation of dextromethorphan selected from the group comprising dextrorphan, D-3-methoxymorphinan and D-hydroxymorphinan, said metabolite being in an amount effective to potentiate anticonvulsant activity of said anticonvulsant compound.

INTERNATIONAL SEARCH REPORT

International Application No. PCT/US88/04539

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [6]

According to International Patent Classification (IPC) or to both National Classification and IPC

INT. CL.[4] A61K 31/44
U.S. CL. 514/282

II. FIELDS SEARCHED

Minimum Documentation Searched [7]

Classification System	Classification Symbols
U.S.	514/85, 282, 398, 680

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]

Category *	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No. [13]
Y	US, A, 4,694,010, (Musacchio et al), 15 September 1987, See entire document	1-25
A	US, A, 4,380,548, (Fleming), 19 April 1983, See entire document	1-25

* Special categories of cited documents: [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search

22 March 1989

Date of Mailing of this International Search Report

18 APR 1989

International Searching Authority

ISA/US

Signature of Authorized Officer

Ellen McAvoy

Form PCT/ISA/210 (second sheet) (Rev.11-87)